IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In Re the Application of: | ) | Group Art Unit: 1644 |
| | ) | |
| LAHN et al. | ) | Examiner: Schwadron, R.B. |
| | ) | |
| Serial No.: 09/826,319 | ) | Confirmation No.: 4155 |
| | ) | |
| Filed: April 3, 2001 | ) | |
| | ) | **FOURTH AMENDED APPEAL BRIEF** |
| Atty. File No.: 2879-80 | ) | |
| | ) | ***SUBMITTED VIA EFS-WEB*** |
| For: "METHOD TO INHIBIT AIRWAY HYPERRESPONSIVENESS USING AEROSOLIZED T CELL RECEPTOR ANTIBODIES" | ) | |

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

This Fourth Amended Appeal Brief is filed in response to Notification of Non-Compliant Appeal Brief mailed January 28, 2009, and in furtherance of the non-final Office Action mailed on April 6, 2007, and the Notice of Appeal filed on July 6, 2007. A Reply to Notification of Non-Compliant Appeal Brief is also submitted herewith. This Fourth Amended Appeal Brief is being filed timely and no fees are believed to be due.

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**TABLE OF CONTENTS**

## I. REAL PARTY IN INTEREST

The real party in interest is **National Jewish Medical and Research Center**, the assignee of record, the Assignment being recorded with the United States Patent Office at Reel/Frame 012070/0760.

## II. RELATED APPEALS AND INTERFERENCES

A prior Appeal Brief was filed in this application on November 20, 2006. The Appeal was dismissed by reopening of prosecution.

## III. STATUS OF CLAIMS

The status of the claims in the application is:

A. TOTAL NUMBER OF CLAIMS IN THE APPLICATION

Claims in the application are: 1-36

B. CURRENT STATUS OF THE CLAIMS:

1. Claims cancelled: 33
2. Claims withdrawn: 3-8
3. Claims pending: 1-32 and 34-36
4. Claims allowed: None
5. Claims rejected: 1, 2, 9-32 and 34-36

C. CLAIMS ON APPEAL

The claims on appeal are: 1, 2, 9-32 and 34-36.

## IV. STATUS OF AMENDMENTS

No amendment was filed subsequent to the final rejection mailed on February 22, 2006 or subsequent to the non-final Office Action mailed April 6, 2007.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

### Claim 1

Claim 1 is directed to method to reduce airway hyperresponsiveness in a mammal that has, or is at risk of developing, airway hyperresponsiveness. (Specification: page 9, lines 2-5; page 18, line 27 to page 19, line 26; page 20, lines 5-17)

The method includes the step of administering to the lungs of the mammal an aerosolized antibody formulation comprising antibodies that selectively bind to a receptor on a T cell selected from: a T cell antigen receptor (TCR) selected from the an αβ TCR and a γδ TCR, CD3, CD4 and CD8. (Specification: page 3, lines 3-19; Table 1; page 11, lines 1-22; page 12, line 4 to page 13, line 11; page 13, lines 12-17; page 37, lines 20-27; Examples 1-6).

The binding of the antibodies to the receptor causes the depletion or inactivation of the T cell. (Specification: page 9, line 23 to page 10, line 9; page 11, lines 24-27; Figs. 2A-2B; Figs. 3A-3B).

The administration of the antibody formulation reduces airway hyperresponsiveness in said mammal. (Specification: page 17, line 18 to page 18, line 26; Example 1, Example 2, Example 3; Figs. 1A-1F)

The administration of the aerosolized antibody formulation affects pulmonary T cell responses in the mammal, while peripheral T cell responses in the mammal are neither substantially stimulated nor substantially inhibited. (Specification: page 10, lines 10-18; Example 5; Fig. 3A-3B).

**Claim 2**

Claim 2 is directed to a method to reduce airway hyperresponsiveness line in a mammal that has, or is at risk of developing, airway hyperresponsiveness. (Specification: page 9, lines 2-5; page 18, line 27 to page 19, line 26; page 20, lines 5-17)

The method includes the step of administering to the lungs of the mammal an aerosolized antibody formulation comprising antibodies that selectively bind to an αβ T cell receptor (TCR). (Specification: page 11, lines 1-22; page 12, lines 4-13 page 13, lines 12-17; page 37, lines 20-27)

The binding of the antibodies to the receptor causes the depletion or inactivation of the T cell. (Specification: page 9, line 23 to page 10, line 9; page 11, lines 24-27; Figs. 2A-2B).

The administration of the antibody formulation reduces airway hyperresponsiveness in said mammal. (Specification: page 17, line 18 to page 18, line 26; Example 1; Figs. 1A-1F)

The administration of the aerosolized antibody formulation affects pulmonary T cell responses in the mammal, while peripheral T cell responses in the mammal are neither substantially stimulated nor substantially inhibited. (Specification: page 10, lines 10-18).

**Claim 16 and Claims 19-23**

Claims 16 and 19-23 are directed to particular embodiments of the invention, wherein said aerosolized antibody formulation is administered at low doses (Specification: Page 10, lines 22-28; page 34, line 9 to page 35, line 6), including a dose of between about 5 μg antibody and about 10 μg antibody per milliliter of formulation (Claim 16), or less than about 40 μg x kilogram$^{-1}$ body weight of the mammal (Claim 19), less than about 1 μg x kilogram$^{-1}$ body weight of the mammal (Claim 20), less than about 0.5 μg x kilogram$^{-1}$ body weight of the

mammal (Claim 21), less than about 0.1 μg x kilogram$^{-1}$ body weight of said mammal (Claim 22), or less than about 20 ng x kilogram$^{-1}$ body weight of the mammal (Claim 23). (Specification: page 6, line 26 to page 7, line 2; page 35, lines 7-28; page 36, lines 20-21; original Claims 16, and 19-23)

**Claim 36**

Claim 36 is directed to method to reduce airway hyperresponsiveness line in a mammal that has, or is at risk of developing, airway hyperresponsiveness. (Specification: page 9, lines 2-5; page 18, line 27 to page 19, line 26; page 20, lines 5-17)

The method includes the step of administering to the lungs of the mammal an aerosolized antibody formulation comprising antibodies that selectively bind to a receptor on a T cell selected from: a T cell antigen receptor (TCR) selected from the an αβ TCR and a γδ TCR, CD3, CD4 and CD8. (Specification: page 11, lines 1-22; page 13, lines 12-17; page 37, lines 20-27)

The binding of the antibodies to the receptor causes the depletion or inactivation of the T cell. (Specification: page 9, line 23 to page 10, line 9; page 11, lines 24-27; Figs. 2A-2B; Figs. 3A-3B).

The administration of the antibody formulation reduces airway hyperresponsiveness in said mammal. (Specification: page 17, line 18 to page 18, line 26; Example 1, Example 2, Example 3; Figs. 1A-1F)

In this method, any stimulation or inhibition of peripheral T cell responses in the mammal after the aerosolized antibody administration is less than about 10% of stimulation or inhibition of the peripheral T cell responses that would be detected if the antibody formulation was administered systemically. (Specification: page 11, lines 14-18).

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole issues on appeal are:

**A.** Whether Claims 1, 2, 9-32 and 34-46 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement; and

**B.** Whether Claims 1, 2, 9-32 and 34-46 are unpatentable under 35 U.S.C. § 103(a) over Lobb et al. (U.S. Patent No. 5,871,734) as evidenced by Arrhenius et al. (U.S. Patent No. 5,869,448) in view of Schramm et al. (*Amer. J. Respir. Cell Mol. Biol.*, **22**(2):218-25 (2000)), Wigzell et al. (U.S. Patent No. 5,958,410) and Krause et al. (U.S. Patent Application Publication No. 2002/0037286).

## VII. ARGUMENT

### A. Rejection of Claims 1, 2, 9-32 and 34-46 Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 9-32 and 34-46 have been once rejected under 35 U.S.C. § 112, first paragraph, on the basis that the claims allegedly fail to meet the requirements of written description.

The rejection reasons that the claims encompass the use of antibodies that bind to T cell receptors (TCR), CD3, CD4 and CD8 from thousands of mammalian species. The rejection argues that while human and mouse counterparts of these molecules were known, there are thousands of counterparts from other mammalian species that were not known and have not been sequenced at the amino acid level. The rejection contends that the skilled artisan cannot envision the detailed structure of the encompassed antibodies and therefore, that conception has not been achieved until reduction to practice has occurred. Further, it is stated that in the instant application, the peptide itself is required. The rejection reasons, "if an inventor is 'unable to envision the detailed constitution of a gene so as to distinguish it from other materials…conception has not been achieved until reduction to practice has occurred'". As controlling precedent, the rejection references: *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991); and *Fiers v. Revel*, 984 F.2d 1164, 1168, 25 USPQ2d 1601, 1604-05 (Fed. Cir. 1993). See the Office Action mailed April 6, 2007, pages 2-3.

The first paragraph of Section 112 of Title 35 of the United States Code requires that:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

To satisfy the written description requirement of this paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 ("applicant must...convey to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention"). What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005). From *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006): "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met...even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure".

Based on the current legal precedent regarding written description, Appellant contends that Claims 1, 2, 9-32 and 34-46 meet the written description requirement of 35 U.S.C. § 112, first paragraph. Arguments are presented below for each claim or group of claims. Claims argued under different subheadings below do not stand or fall together.

**Claims 1, 9-32, and 34-46**

Appellants submit that the rejection of the claims on the basis of failure to meet the written description requirement is improper and contravenes the current legal precedent. Specifically, the rejection reasons that the skilled artisan cannot envision the detailed structure of the antibodies encompassed by the claims because specifically, a peptide is allegedly required (apparently a peptide of an αβ T cell receptor (TCR), a γδ TCR, CD3, CD4 or CD8). Therefore, the rejection states that conception has not been achieved until reduction to practice has occurred. Appellants submit that the rejection is requiring that the specification teach what is conventional or well-known in the art with respect to the recited proteins and antibodies, which is contrary to court decisions more recent than those cited in the rejection. The more recent legal precedent clarifies the standard for written description.

More particularly, the rejection refers to case law in which the discovery of a gene function or structure itself was at issue. For example, in *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), the claims at issue recited a cDNA encoding human insulin, where only a cDNA encoding rat insulin had been described. *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) concerns a claim to a gene encoding human erythropoietin, where such gene had not yet been cloned or sequenced. *Fiers v. Revel*, 984 F.2d 1164, 1168, 25 USPQ2d 1601, 1604-05 (Fed. Cir. 1993) concerns claims to a gene encoding human fibroblast interferon-beta polypeptide, who was the first to invent the isolated sequence, and specifically, that conception of the sequence did not occur until the sequence was obtained.

However, the fact patterns in the cases cited by the rejection do not apply to the fact pattern in the present application, which claims a new use for a molecule that was already known in the art. Specifically, Appellants are not claiming the discovery of any of an αβ T cell receptor (TCR), a γδ TCR, CD3, CD4 and CD8, nor antibodies that bind to such proteins, but rather, a novel method of using such antibodies. It is submitted that the present specification provides a written description of this invention that is sufficient to establish that the inventors were in possession of the invention at the time of filing.

> "The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge...When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh." *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005).

Indeed, as stated in *Capon v. Eshhar*, *ibid.*:

> "None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen, or Enzo Biochem, require a re-description of what was already known. In *Lilly, 119 F.3d at 1567*, the cDNA for human insulin had never been characterized. Similarly in *Fiers, 984 F.2d at 1171*, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a "wish" or research "plan." In *Amgen, 927 F.2d at 1206*, the court explained that a novel gene was not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In *Enzo Biochem, 296 F.3d at 1326*, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003)* the court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.""

Appellants submit that the same reasoning used in *Capon v. Eshhar* should be applied to the present claims. Indeed, all of the *same* proteins that are subject of the present rejection were included in the written description rejection at issue in *Capon v. Eshhar* (*i.e.,* the α, β, γ or δ chain of a T cell receptor, CD3, CD4 and CD8).

The present specification teaches that each of the proteins recited in the claims were known in the art at the time of the invention, and further teaches that antibodies binding to each of the cited proteins were known in the art at the time of the invention, including antibodies to the murine and human forms of the proteins, with provision of at least one commercial source for such antibodies. More particularly, the specification teaches on page 3, lines 3-19, that antibodies against the T cell antigen receptor (TCR), CD3, and CD4 were known and references publications and patents that describe antibodies against CD3, the TCR α or β chains, and CD4. Table 1 provides a list of antibodies that were in clinical application at the time of the invention, including antibodies against CD3 and CD4, and including humanized antibodies. Page 13, lines 12-17 teaches that "Antibodies against various T cell receptors useful in the present invention are known in the art. For example, antibodies against murine TCR-β, TCR-δ, and TCR-Vγ1 are described in the examples section. Antibodies against murine and human TCR-β, TCR-α, TCR-δ, TCR-γ, CD3, CD8 and CD4 are known in the art and are publicly available and referenced through Pharmingen (San Diego, CA), for example." Examples 1-6 provide examples of antibodies against TCR-αβ and TCR- γδ. The state of the art at the time of the invention was such that each of the recited proteins and antibodies directed against such proteins were known. Indeed, the rejection acknowledges that the murine and human counterparts of these molecules were known at the time of the invention.

However, the rejection implies that in order to meet the written description requirement, the specification must describe each and every permutation of an antibody that binds to such proteins, including all proteins from every mammalian species. Appellants disagree. The specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention.

Referring again to *Capon v Eshhar*:

> "It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See *In re Angstadt, 537 F.2d 498, 504 (CCPA 1976).*"

The specification provides not only general teachings regarding the antibodies and proteins to which they bind, but also working examples describing the invention using several different antibodies, and references specific examples of such antibodies in the scientific and patent literature, as well as commercially available antibodies covering all of the claimed embodiments.

> "Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art", and "Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences…satisfaction of the written description requirement does not require either the recitation or incorporation by reference…of such genes and sequences. *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006).

Current case law also further addresses written description with respect to antibodies. "Disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen." *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004). In *Noelle v. Lederman*, a generic claim to an antibody was deemed not to meet the written description requirement because only the mouse version of the protein to which it bound was known. In contrast, in the present case, and at a minimum by the rejections' own reasoning, both human and mouse antigens were known at the time of the invention. A brief review of a few of the patents described on page 3 of the present specification, *e.g.,* U.S. Patent No. 6,171,799 (describing in detail both αβ TCR and γδ TcR), shows that the art at the time of the invention had detailed knowledge of the structure of these proteins, as well as antibodies that bind to these proteins. Thus, at the time of the invention, the antigens to which the recited antibodies bind had been fully characterized and were known in the art with respect to many different mammalian species.

Accordingly, it is submitted that the present specification meets the written description requirement, and Appellants respectfully request that the Board withdraw the rejection of Claims 1, 9-32, and 34-46 under 35 U.S.C. § 112, first paragraph.

**Claim 2**

With respect to Claim 2, Appellant notes that this claim is directed to the elected species of αβTCR, whereas Claim 1 in the group of claims above is directed to all species, including non-elected species that were previously rejoined in the Office Action mailed September 8, 2005, and then subsequently restricted again in the Office Action mailed February 22, 2006.

Appellant's arguments against the rejection of Claim 2 under 35 U.S.C. § 112, first paragraph, are essentially the same as the arguments presented above in view of Claim 1, although such arguments are in the case of Claim 2 directed exclusively to the elected species. However, in the event that Claim 1 falls as a result of consideration of non-elected species in Claim 1, Appellant expressly submits that Claim 2, as well as dependent Claims 9-15, 17-18, and 24-35, to the extent they depend from Claim 1 with respect to the elected invention of αβTCR as recited in Claim 2, do not stand or fall together with Claim 1.

With particular regard to αβTCR, it is Appellants' position that αβTCR proteins were well known in the art at the time of the invention, as discussed in detail in the paragraphs above, and accordingly, were fully characterized to the point that an antibody that binds to an αβTCR was also well known. Moreover, "It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See *In re Angstadt, 537 F.2d 498, 504 (CCPA 1976).*" The working examples of the specification describe the use of an antibody that binds to αβTCR in the method of the invention, and it is believed that the specification has fully met the written description requirement of 35 U.S.C. § 112, first paragraph.

In view of the foregoing discussion, Appellants respectfully request that the Board withdraw the rejection of Claim 2 under 35 U.S.C. § 112, first paragraph.

**B. Rejection of Claims 1, 2, 9-32 and 34-46 Under 35 U.S.C. § 103(a)**

Claims 1, 2, 9-32 and 34-46 have been at least twice rejected under 35 U.S.C. § 103(a) over Lobb et al. (U.S. Patent No. 5,871,734) as evidenced by Arrhenius et al. (U.S. Patent No.

5,869,448) in view of Schramm et al. (*Amer. J. Respir. Cell Mol. Biol.*, 22(2):218-25 (2000)), Wigzell et al. (U.S. Patent No. 5,958,410) and Krause et al. (U.S. Patent Application Publication No. 2002/0037286).

The rejection reasons that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to create the claimed invention because Lobb et al. teach aerosol administration of an antibody that binds T cells to treat asthma and Schramm et al. teach that intravenous (i.v.) administration of a different antibody that binds T cells (anti-TCR αβ) can be used to treat asthma. Motivation is alleged because Lobb et al. teach that the antibody can be administered in a variety of art known routes including aerosol. Motivation is further alleged on the basis that Krause et al. teach that antibodies that inhibit T cell activation are preferably administered by pulmonary aerosol and Wigzell et al. teach that pathologic T cells found in the lungs can be treated via intrapulmonary administration of anti-TCR antibody. It is further reasoned that a neutralizing antibody would be used in the claimed method because Schramm et al. teach that asthma symptoms are reduced in the absence of TCRαβ T cells. It is reasoned that with respect to the particular recited dosages of formulation or dosage per weight, a "routineer" would initially test a wide variety of different dosages in order to determine the smallest effective dosage, that the antibody would be administered by a "routineer in conjunction with art known treatments for asthma, and that the antibody would have been administered either before or during asthma symptoms. Finally, the rejection reasons that Lobb et al. teach that the effect can be achieved without detectable blood levels of antibody wherein the aerosol administered antibody would therefore not substantially effect peripheral immune T cell responses. See, *e.g.*, Office Action mailed April 6, 2007 (April 6 Office Action), page 5, which is repeated on page 6.

With respect to the individual references, the rejection further reasons that Lobb et al. teach the use of antibody against VLA-4 to treat asthma, and Arrhenius et al. is cited as teaching that VLA-4 is a receptor on T cells. Lobb et al. is further cited for the following teachings: airway hyperresponsiveness occurs in asthma; the use of humanized anti-VLA-4 antibody and a monovalent antibody; the anti-VLA4 antibody does not stimulate T cell activation (via an alleged teaching that the antibodies inhibit VLA-4 function); the use of antibody dosages encompassed in the instant Claims 18 and 19; administration of antibody by a nebulized spray; the method of instant Claim 27; the methods of instant Claims 28, 31 and 32; "Lobb et al. teach that the effect seen can be achieved without detectable blood levels of antibody (see column 12, last paragraph) wherein the antibody would not therefore substantially effect peripheral immune function (e.g. because it was not present in the blood)"; the use of the method in humans; and that the method resulted in a 70% decrease in inhibition of late phrase response. The rejection also states that "Lobb et al. disclose: 'For instance, to the extent that the beneficial effects reported herein are due to the inhibition of leukocyte recruitment to VCAM-1 expressing endothelium...' (column 8, last paragraph):, in support of the argument that Lobb et al. contemplate that their method involves inhibition of leukocytes including T cells. The rejection acknowledges that Lobb et al. does not teach the use of anti-TCRαβ antibodies. Schramm et al. is cited for an alleged teaching of the use of intravenous anti-TCR antibodies to treat asthma. The rejection argues that there is no teaching in Schramm et al. that a complete systemic depletion of an entire T cell subset form an animal is required in the antibody treated animals. Krause et al. is cited as teaching that antibodies that inhibit T cell activation are preferably

administered by pulmonary aerosol. Wigzell et al. is cited as teaching that pathologic T cells found in the lungs can be treated via intrapulmonary administration of anti-TCR antibody.

To establish a *prima facie* case of obviousness: (1) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) Second, there must be a reasonable expectation of success; (3) Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP § 2143-§2143.03. An Examiner has the initial burden of establishing a *prima facie* case of obviousness before the burden shifts to the applicant to show otherwise. See, e.g., In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> "whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure." *In re Dow Chemical*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Based on the required showing set forth by the Federal Circuit, Appellant contends that a *prima facie* case of obviousness has not been established in the present case. Arguments are

presented below for each claim or group of claims. Claims argued under different subheadings below do not stand or fall together.

**Claims 1, 9-15, 17-18, and 24-35**

Appellant submits that the combination of references fails to teach or suggest the use of an *aerosolized antibody* having one of the particularly recited receptor specificities (*i.e.,* αβ TCR, γδ TCR, CD3, CD4 or CD8) to *reduce airway hyperresponsiveness*, wherein the binding of the antibody to the receptor *causes the depletion or inactivation of the T cell* and wherein the administration of the aerosolized antibody formulation *affects pulmonary T cell responses in the mammal, while peripheral T cell responses in the mammal are neither substantially stimulated nor substantially inhibited.* It is also Appellant's position that the combination of references fails to provide the requisite motivation to combine the references to arrive at the claimed invention and further, fails to provide a reasonable expectation of success to arrive at the claimed invention as claimed in Claims 1, 9-15, 17-18, and 24-35.

The rejection is primarily based on the combination of Lobb et al. and Schramm et al., where the rejection asserts that Lobb et al. teach aerosol administration of an antibody that binds T cells to treat asthma and Schramm et al. teach that a different antibody that binds T cells (anti-TCRαβ) can be used to treat asthma. However, Appellant submits that this combination, even when combined with the other references of Krause et al., Arrhenius et al. and Wigzell et al., fail to teach or suggest the invention as claimed in Claims 1, 9-15, 17-18, and 24-35. Furthermore, there is no suggestion or motivation found in the references themselves or in the art at the time of the invention to make the combination as the rejection has done. It is the rejection's apparent position that it would be obvious to substitute the antibody of Schramm et al. into a method of

Lobb et al., and that based on the teachings of Wigzell et al., Krause et al. and Schramm et al., one of skill in the art would be motivated to do so and would expect success in making the substitution. However, Appellant submits that there is no teaching, suggestion or motivation provided by any of the cited references to substitute the anti-VLA-4 antibody of Lobb et al. with the anti-TCRαβ antibody of Schramm et al., or *vice versa*, even when combined with the other three references. Indeed, neither of Lobb et al. or Schramm et al. attempts to extend its teachings beyond the specific antibody having the specific specificity described in the respective reference.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggesting supporting the combination. ACS Hospital Systems v. Montofiore Hospital, 221 USPQ 929, 933 (Fed.Cir. 1974). "A statement that modifications of the prior art to meet the claim limitations would have been 'well within the ordinary skill of the art at the time the invention was made', because the cited references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)." MPEP 2143.01.

With these standards in mind, first, Appellant reviews the rejection's allegation that Lobb et al. teach aerosol administration of an antibody that binds T cells to treat asthma, and the use of this alleged teaching as a basis for including Lobb et al. in the combination of cited references. Lobb et al. is directed to the use of antibodies recognizing VLA-4 integrin, which is a cell adhesion receptor that binds to adhesion molecules such as VCAM-1 (see Arrhenius et al., col. 1, line 54 to col. 2, line 11). Appellant agrees with the rejection that Arrhenius et al. teaches that

VLA-4 is a receptor found on T cells, which is all that Arrhenius is alleged to contribute to the combination of references. However, Appellant further notes, as supported by Arrhenius et al. (col. 1, lines 54-65), and by Lobb et al. (col. 2, lines 60-62), anti-VLA4 binds to *a variety of cell types* in addition to T cells, including B lymphocytes, natural killer cells, monoctyes, basophils and eosinophils. This teaching is relevant to the interpretation of the teachings of Lobb et al., as discussed below. Claim 1 of the present invention is directed to the use of aerosolized antibodies that selectively bind to a receptor on a T cell selected from: an αβ T cell antigen receptor (TCR), a γδ TCR, CD3, CD4 and CD8 (which are all *T cell-specific* receptors), to reduce airway hyperresponsiveness in a mammal.

One important aspect of the rejection reasons that because Lobb et al. teach that anti-VLA4 "treats asthma" in a mammal, and because VLA4 is found on T cells, Lobb et al. accordingly provide a teaching sufficient to combine this reference with a second reference (Schramm et al.) that describes a *different* antibody that binds to a *different* receptor on T cells, expecting that such different antibody will also be useful in the method of Lobb et al. First, it is Appellant's position that one of skill in the art reviewing Lobb et al. would not conclude that the effects on airway hyperresponsiveness observed in Lobb et al. are due to an action of the antibody on T cells, since that conclusion is not presented in Lobb et al. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Appellant submits that there is absolutely no teaching or even a suggestion in Lobb et al. that the effects of the anti-VLA4 on airway hyperresponsiveness or any other aspect of asthma, *regardless* of whether the antibody can bind to T cells, are due to any action of the antibody on T cells (*i.e.,* T lymphocytes). Initially, it is noted that a variety of cell types, including basophils, eosinophils, lymphocytes, neutrophils, and monocytes, including macrophages, can be generically referred to as leukocytes or white blood cells, leukocytes being the general term used in Lobb et al. Lymphocytes are a specific subset of leukocytes and include T and B lymphocytes. It is Appellant's position that Lobb et al. teach that the observed effects of anti-VLA4 was on neutrophil and eosinophil recruitment. Indeed, the data of Lobb et al. do not indicate that anti-VLA4 had *any* effect on lymphocyte numbers or recruitment, and upon review of Fig. 4 of Lobb et al., it appears as though anti-VLA4 actually *increased* the lymphocytes in the lungs of the animal (Fig. 4B of Lobb et al.). Lobb et al. provide no other relevant discussion of lymphocytes and no specific mention of T lymphocytes in the patent. However, Lobb et al. provide a *clear teaching* that anti-VLA4 administration caused a significant inhibition of the recruitment of neutrophils and eosinophils to the lung (column 3, lines 4-7; col. 8, line 64 to col. 9, line 2 (note in particular the reference to blocking interactions with *endothelial* cell receptor molecules); Figure 4, and column 12, lines 10-21), which are the only leukocytes to which Lobb et al. appear to attribute the inhibition of the various observed responses. Lobb et al. specifically teach that binding of anti-VLA-4 to leukocytes (*e.g.*, eosinophils and neutrophils) inhibits the migration of such cells to VCAM-1 expressing endothelium, and propose that "antibodies that interfere with the adhesion between leukocyte antigens and *endothelial cell* receptor molecules may be advantageous" (emphasis added) (col. 8, line 63 to col. 9, line 2). Again, as discussed

above, Lobb et al., as supported by Arrhenius et al., teach that VLA-4 is present on a variety of different cell types, including eosinophils, which are important mediators of inflammation in asthma. Accordingly, at a minimum, the effects of anti-VLA-4 appear from Lobb et al. to be largely attributable to the action of the antibody on neutrophils and eosinophils, and there is no teaching or suggestion in Lobb et al., explicit or implicit, that the anti-VLA-4 antibody depleted or inactivated T lymphocytes, or that an effect on T cells contributed at all to the observed responses after administration of the antibody.

In contrast, the antibody of the present invention, which binds to a T cell-specific receptor, removes (depletes) and/or inactivates a small and relevant population of T cells which are directly involved in the allergic inflammatory response in the lung. Lobb et al. do not teach or suggest any antibody other than one that binds to VLA-4 or LFA3, which are both adhesion molecules, nor any other mechanism of inhibiting allergic inflammation other than inhibiting the migration of leukocytes (specifically, neutrophils and eosinophils) to lung tissue. Therefore, Lobb et al. can not provide motivation to switch to a different antibody or different mechanism of action, including the one taught by Schramm et al., even when viewed with Wigzell et al. and Krause et al.

Accordingly, it is Appellant's position that Lobb et al. do not teach an aerosolized antibody that binds to a T cell receptor and causes the depletion or inactivation of the T cell, nor do Lobb et al. teach that one should modulate T cells to treat asthma, nor would the teachings of Lobb et al. motivate one of skill in the art to look at the modulation of T cells to treat asthma or airway hyperresponsiveness. At best, the teachings of Lobb et al. would suggest that one should look at methods of targeting *eosinophils or neutrophils* to treat asthma, and could further suggest

that modulation of T cells is not necessary, or is not effective using an anti-VLA4 antibody. This is a *teaching away* from the present invention. Indeed, the only connection between the anti-VLA4 and an action on T cells appears to come from the rejection, and not the teachings of Lobb et al., and would therefore appear to be based on the teachings of the instant specification. The rejection therefore appears to use hindsight in making the obviousness rejection in that the rejection attempts to find each element of the pending claims in the prior art, and then reasons that it is easy to reassemble these elements into the invention; however "it is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teaching of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *Interconnect Planning Corp. v. Feil*, 774 F2d 1132,1138, 227 USPQ 543,547 (Fed. Cir. 1985). "As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co. v. Teleflex Inc. (KSR), 127 S. Ct. 1727*; *167 L. Ed. 2d 705*; 82 USPQ2d 1385 (2007).

Appellant's position and the teachings of Lobb et al. directly rebut the rejection's position that Lobb et al. provide any teaching or motivation to make the combination with Schramm et al., Wigzell et al., and/or Krause et al. The rejection's position is clearly not a reasonable

conclusion based on the Lobb et al. disclosure and would not be the conclusion of one of skill in the art with the reference of Lobb et al. before him.

Appellant further submits that the VLA-4 integrin of Lobb et al. is a completely different cell surface molecule than the recited T cell-specific receptors, such that *even if* one considers binding of such antibody to a T cell, antibodies that bind to VLA-4 will be expected to have different effects on a T cell than antibodies that bind to one of the T cell receptors recited in the instant claims. For example, anti-VLA4, as taught by Lobb et al. and discussed above, can reduce recruitment of cells to a tissue. In contrast, the recited T cell receptor antibodies are directed against T cell activation receptors and coreceptors, and are depleting or inactivating antibodies (*e.g.,* blocking antibodies are not included). However, the rejection appears to base motivation for combining Lobb et al., Schramm et al., Krause et al. and Wigzell et al. at least in part on the argument that if one antibody that binds to T cells reduces airway hyperresponsiveness, then all antibodies that bind to T cells will reduce airway hyperresponsiveness, regardless of the target protein or mechanism of action, and further, that results with aerosolized antibodies can necessarily be extrapolated from results using systemically administered antibodies, and *vice versa*.

Using this rationale, one of skill in the art should therefore expect that an antibody that binds to LFA-3 would reduce airway hyperresponsiveness, since LFA-3 is another adhesion protein, indeed a protein of similar function to VLA4, that is known in the art to be expressed on T cells, among other cells. However, Lobb et al. demonstrates that anti-LFA3 did not reduce airway hyperreponsiveness when administered to an animal. Referring to Example 2 of Lobb et al. (col. 12, line 37 to col. 13, line 7), where aerosolized anti-VLA-4 administration (antibody

HP1/2) was compared to aerosolized anti-LFA-3 administration (antibody IE6), Lobb et al. clearly teaches that administration of aerosolized anti-LFA-3 had **no effect** on airway hyperresponsiveness.

Therefore, the argument that one could simply substitute a different antibody into the specific anti-VLA4 method of Lobb et al. is not correct and is clearly rebutted in the references of record. Such an argument lacks common sense in view of the clear teaching away from that position in Lobb et al. It is clear from this example alone that the combination of elements inferred by the rejection would not be expected to yield predictable results.

Furthermore, Appellant submits that the previously submitted publication by Fahy et al. (enclosed in Evidence Appendix) rebuts the rejection's line of reasoning that it would be expected that a systemically delivered antibody of Schramm et al. would be useful in the method of aerosolized delivery of Lobb et al., because Fahy et al. shows that provision of a therapeutic effect by administration of antibodies systemically does not necessarily mean that the same effect will be provided when the same antibody is administered by aerosol. As discussed on page 5, lines 10-16, Fahy et al. used aerosolized anti-IgE to test whether direct delivery of the antibody to the airway would have the same effect as the systemic delivery of the antibody, which had already been shown to attenuate early and late phase responses to inhaled allergen (Fahy et al., 1999, *Am. J. Respir. Crit. Care Med.* **160**:1023-1027). Fahy's experiment demonstrated that the aerosolized anti-IgE did not attenuate the airway responses to inhaled allergen and in at least one subject, the antibody proved to be immunogenic. Therefore, this experiment shows that, based on the art, one cannot assume that achievement of a therapeutic effect by administration of an antibody systemically can be extrapolated to aerosol

administration of the same antibody. The argument can be taken a step further in that the rejection has attempted in the present combination of references to compare two *completely different* antibodies on this basis (*i.e.,* antibodies with different antigen specificities), which makes prediction of effects even more unreasonable. Therefore, the rejection's argument that one can take the results of Lobb et al. and thereby predict a result using the antibody of Schramm et al. is not fairly based on scientific evidence. Moreover, the teachings of Wigzell et al. and Krause et al. do not contradict the findings of Fahy et al., as neither of Wigzell et al. or Krause et al. had any actual demonstration of the administration of an antibody in aerosol form (discussed in more detail below).

The rejection reasons on page 9 of the April 6 Office Action that: "Fahy et al. hypothesize that the antibody might have been more immunogenic via the aerosol route, but the successful results of Lobb et al. would tend to disagree with this hypothesis", which is speculation put forth by the rejection itself that is not supported by evidence. As discussed above, Lobb et al. investigated the effects of an antibody with a completely different antigen specificity (VLA-4 versus IgE) on airway hyperresponsiveness and provided results that are in contrast to Fahy et al., illustrating the unpredictability of aerosol administration of antibody. The rejection further reasons on page 9 of the April 6 Office Action that the most logical explanation for the results in Fahy et al. "is that their antibody was not effective was because it was antibody that bound a soluble antigen (IgE) present in large quantities in the vascular space wherein said IgE acted as a 'sink of IgE'", and concludes that the results of Fahy et al. are not germane to the claimed invention. Appellants do not see how Lobb et al., directed to a different antigen specificity than that claimed is relevant to the claimed invention, while Fahy et al. is somehow

not germane to the invention. Moreover, as discussed above, Lobb et al. teach that aerosol delivery of LFA-3, a protein of the same general type as VLA-4, did not inhibit airway hyperresponsiveness. Based on the reasoning in the rejection, including the rationale for the dismissal of Fahy et al. as being irrelevant, the aerosol administration of LFA-3 would have been predicted to inhibit airway hyperresponsiveness; however, it did not.

Given that Appellant finds no basis in Lobb et al. by way of a teaching, suggestion or motivation for making the combination with Schramm et al. and/or the other cited references, Appellant now reviews the rejection's contention that Schramm et al. teach that anti-TCRαβ can be used to treat asthma, which is the rejection's stated basis for the combination of Schramm et al. with Lobb et al. Appellant submits that Schramm et al. do not teach that anti-TCRαβ can be or should be used *to treat asthma*, and more particularly, Appellant submits that Schramm et al. do not teach that *any antibody*, including anti-TCRαβ, can be used to reduce *airway hyperresponsiveness*, which is the subject of the instant claims. As defined in the present specification on page 14, lines 7-9, "'airway hyperresponsiveness' or 'AHR' refers to an abnormality of the airways that allows them to narrow too easily and/or too much in response to a stimulus capable of inducing airflow limitation". Appellant emphasizes that this is the subject of the claimed invention (*i.e.,* the reduction of airway hyperresponsiveness in a mammal). In contrast, the only teaching of Schramm et al. related to antibodies is a teaching that the *systemic depletion* in an animal of αβ T cells using anti-TCRαβ, or the *systemic depletion* of γδ T cells using anti-γδ, significantly reduces eosinophils, and to a lesser extent, lymphocytes and macrophages, in bronchoalveolar lavage fluid (BALF) (see Figure 1). These are the *only* experiments in Schramm et al. that use antibodies; the remaining experiments are performed in

*TCR knockout mice*. With respect to airway hyperresponsiveness, which is the subject of the instant claims, Schramm et al. do not teach that *any* antibody administered by *any* route can reduce airway hyperresponsiveness, nor do Schramm et al. determine the effect of complete αβTCR depletion on airway hyperresponsiveness using the knockout mice. The only experiments directed to airway hyperresponsiveness in Schramm et al. use wild-type mice or TCR δ-/- mice (*i.e.,* TCR δ knockout mice). Schramm et al. specifically state on page 222, col. 2, last sentence of top paragraph "Methacholine responses were not studied in TCRβ -/- mice...".

Moreover, it is Appellant's position that Schramm et al. lacks any teaching or suggestion to use any antibodies for the treatment of asthma. Schramm et al. teaches that anti-αβTCR, administered *systemically*, reduces the accumulation of various cells in BALF, but it is Appellant's position that this is not a teaching that such an antibody could or should be used to treat asthma. Schramm et al. is a research publication that is primarily directed to determining the role of γδ T cells in asthma, and also to dissect the roles of the two T cell subsets (αβ and γδ). Appellant submits that Schramm et al. do not teach or suggest the therapeutic use of *any* antibodies for the treatment of asthma. In general, Appellant does not find any teaching in Schramm et al. regarding how asthma should be treated. Indeed, complete, systemic depletion of T cells, or substantial depletion of T cells, which is the only use of the antibodies described in Schramm et al., would *not* be viewed by one of skill in the art as a therapeutic approach to treatment of a disease, including airway inflammation and/or hyperresponsiveness, because complete, systemic depletion of a major arm of the immune system as a therapy would have clear, undesirable consequences for the animal.

On page 7 of the April 6 Office Action, the rejection argues that "there is no teaching in Schramm et al. that a complete systemic depletion of an entire T cell subset from an animal is required in the antibody treated animals". First, the only experiments described in Schramm et al. pertain to the use of either TCR knockout mice (*i.e.,* there is a "complete" deletion of T cell subset to which the knockout is directed - see, *e.g.,* page 219, col. 1, first paragraph) and the use of anti-TCR antibodies that deplete the animal of the relevant T cells (see, *e.g.,* page 220, col. 2, last paragraph; "Similar findings were observed in mice depleted of TCRγδ or TCRαβ cells by treatment with monoclonal antibodies (Figure 1)"). Therefore, even if the antibodies do not *completely* deplete the mice of the relevant T cells, clearly, the intent of Schramm et al. is to compare the knockout results to antibody depletion; whether or not complete depletion is achieved via antibody administration. Referring to Figure 1 of Schramm et al., the antibody depletion of T cells is significant, and it is Appellant's position that systemic depletion of T cells, whether complete or substantial, would *not* be viewed by one of skill in the art as a therapeutic approach to treatment of a disease.

Second, and perhaps more relevant to the issue at hand, Appellants refer to the discussion above and again emphasize that *in the antibody-treated animals*, Schramm et al. do not evaluate airway hyperresponsiveness; only eosinophil and other cell accumulation in BALF is evaluated (see Figure 1 of Schramm et al.). Moreover, even *when* airway hyperresponsiveness is evaluated, this is only done in the *γδ TCR knockout mice,* and not in the αβ TCR knockout mice (see page 222 of Schramm et al., "Methacholine responses were not studied in TCRβ-\- mice because every animal studied failed to mount an inflammatory immune response to OVA"). Therefore, there is no teaching in Schramm et al. of the effects of the depletion of T cells having

an αβ TCR (complete or partial), by any means, on airway hyperresponsiveness. Accordingly Schramm et al. simply does not teach the use of any antibody against any T cell protein to inhibit airway hyperresponsiveness.

Moreover, Schramm et al. do not teach or suggest the use of aerosolized antibodies or the administration of antibodies to the lung of an animal. One does not learn from the teachings of Schramm et al. that one could or should therapeutically deplete or inactivate the pulmonary T cells in an animal to treat airway hyperresponsiveness in the animal, and moreover, one can not learn from the teachings of Schramm et al. that one can deplete pulmonary T cells and treat airway hyperresponsiveness without substantially affecting peripheral T cells in the animal. Schramm et al. is not at all concerned with therapeutic approaches to reducing airway hyperresponsiveness, nor to any other T cell-expressed proteins, such as the VLA-4 integrin of Lobb et al. Thus, there is no teaching, suggestion, motivation or expectation of success provided by Schramm et al. to make or use the present invention, even when combined with Lobb et al., alone or in combination with the other references. Accordingly, it is submitted that the rejection's basis for the combination of Schramm et al. with Lobb et al. fails, since Appellant finds no teaching or suggestion in Schramm et al. teach that anti-TCRαβ, including aerosolized anti-TCRαβ, nor anti-TCRγδ, including aerosolized anti-TCRγδ, should be used to treat asthma or specifically, to reduce airway hyperresponsiveness.

Having provided arguments against the rejection's reasoning for combining Lobb et al. and Schramm et al., Appellant now addresses the rejection's stated rationale for the inclusion of Wigzell et al. and Krause et al. in the combination.

The rejection contends that Wigzell et al. provide motivation to combine Lobb et al. and Schramm et al. by teaching that pathologic T cells found in the lungs can be treated via intrapulmonary administration of anti-TCR antibody. However, it is submitted that Wigzell et al. is unrelated to the teachings of either of Lobb et al. or Schramm et al. and do not provide any motivation to combine these two references. Wigzell et al. characterizes T cells from the lungs of patients with sarcoidosis, which is an inflammatory disease in which granulomas form on various tissues and organs, including the lung, lymph nodes, skin, and eyes (col. 1, lines 18-21). Therefore, sarcoidosis, and its treatment, are not limited to the lungs. Wigzell et al. identify a particular subset of T cell receptors that appear to be increased in patients with sarcoidosis, and suggest making an antibody to this particular T cell receptor to treat this specific disease. Appellant submits that sarcoidosis is not related to asthma or airway hyperresponsiveness, nor is the identification of the particular T cell subset by Wigzell et al. relevant to asthma or airway hyperresponsiveness, and therefore, there is no teaching, suggestion or motivation in Wigzell et al. to that would cause one of skill in the art to include this reference in the cited combination or in particular, to combine Lobb et al. with Schramm et al. The rejection emphasizes that Wigzell et al. teach intrapulmonary administration of TCR antibody as a basis for motivation. However, intrapulmonary administration is listed among a larger group of "known routes" (col. 13, lines 22-25), and there is nothing in this generic teaching that would lead one of skill in the art reading Wigzell et al. to combine the references of Lobb et al. and Schramm et al. Indeed, since Lobb et al. teach aerosolized administration of anti-VLA4, it is not clear how a teaching by Wigzell et al. that antibodies can be administered by intrapulmonary routes provides any information at all, and particularly, with respect to the combination of Lobb et al. with Schramm et al. Moreover, there

is no demonstration of the actual administration *in vivo* of any antibody in any form in Wigzell et al., including by aerosol, and so regardless of whether or not Wigzell et al. list various possible routes of administration for antibodies, one of skill in the art has absolutely no expectation that aerosol administration of the Wigzell et al. antibody to treat *any* disease, including sarcoidosis, would be successful. Appellant has provided examples above of instances in which systemic administration did not equate to pulmonary administration, and in which results with one antibody did not equate to results with a different antibody. It is Appellant's position that Wigzell et al. is devoid of any teaching that would remedy the deficiencies of the combination of Lobb et al. and Schramm et al. as discussed above, even in view of Krause et al. and/or Arrhenius et al.

Similarly, the rejection asserts that Krause et al. teach that antibodies that inhibit T cell activation are preferably administered via pulmonary aerosol, which allegedly provides motivation to combine Lobb et al. and Schramm et al. Krause et al. teaches the identification of a protein associated with actin cytoskeletal reorganization called "Fyb/SLAP", which, as with the VLA4 of Lobb et al., is not T cell-specific (the protein is expressed also by macrophages, platelets, and perhaps other hematopoietic cells). Krause et al. teach that one may produce an antibody that selectively binds to Fyb/SLAP and administer the antibody to an animal to regulate cytoskeletal reorganization in the animal. In teaching administration of the therapeutics of their invention, Krause teach a variety of routes, similar to Wigzell et al, although Krause et al. states a preference for pulmonary aerosol delivery for the Fyb/SLAP antibodies. However, Appellant submits that regulation of cytoskeletal reorganization is not related to asthma or airway hyperresponsiveness, nor is the antibody described by Krause et al. specific for T cells, and

therefore, there is no teaching, suggestion or motivation in Krause et al. to combine this reference with Lobb et al. and/or Schramm et al. and/or Wigzell et al. Furthermore, the antibody of Krause et al. is not T cell-specific and is a blocking antibody (see section 0008, 0104, 0105), which is not an antibody that binds to any of the recited T cell receptors and is not an antibody that depletes or inactivates T cells, further removing this reference from any relevance to the claimed invention, even when combined with the other references. Finally, since Lobb et al. teach aerosolized administration of anti-VLA4, it is not clear how a teaching by Krause et al. that antibodies can be administered by pulmonary aerosol routes provides any information at all, and particularly, with respect to the combination of Lobb et al. with Schramm et al. As with Wigzell et al., Krause et al. provide no actual demonstration of the administration of any antibody in any form, including by aerosol, and so regardless of whether or not Krause et al. teach that one route of administration is intrapulmonary, one of skill in the art has absolutely no expectation that aerosol administration of the Krause et al. antibody to treat *any* disease would be successful. It is Appellant's position that Krause et al. is devoid of any teaching that would remedy the deficiencies of the combination of Lobb et al. and Schramm et al. as discussed above, even in view of Wigzell et al. and/or Arrhenius et al.

As will be recognized, claims cannot be found obvious unless the prior art teaches or suggests making the claimed product or process and that there is a reasonable expectation of success at doing so. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir., 1991) (The teaching or suggestion to make the claimed combination or modification and the reasonable expectation of success must both be found in the prior art).

In summary, Lobb et al. does not teach or suggest that anti-VLA4 reduces airway hyperresponsiveness by acting on T cells, but instead teaches the use of anti-VLA-4 to inhibit migration of neutrophils and eosinophils (without any showing of an effect on T cells, other than an *increase* in lymphocytes), and further, Lobb et al. additionally teaches that aerosol administration of another antibody that can bind to T cells (among other cells), anti-LFA3, has no effect on airway hyperresponsiveness. Accordingly, this reference cannot provide any teaching, suggestion, motivation or expectation of success at using a T cell-specific antibody that is directed to a completely different antigen and that operates by a completely different mechanism for the treatment of asthma or particularly, airway hyperresponsiveness, regardless of the route of administration. Schramm et al. can not remedy the deficiencies of Lobb et al., because Schramm et al. provides absolutely no connection to the anti-integrin VLA4 antibody, and particularly, because Schramm et al. does not provide any teaching, suggestion, or expectation of success of treating asthma or reducing airway hyperresponsiveness using any antibody that binds to T cells delivered by any route, because there is no teaching or suggestion in Schramm et al. of the use of such an antibody for such a purpose. Wigzell et al. and Krause et al. are not directed to asthma or airway hyperresponsiveness at all, Krause et al. does not describe a T cell-specific antibody, and neither reference provides any demonstration that an antibody administered by any route will have any therapeutic effect on any disease. Accordingly, the combination of references fails to provide sufficient teaching, suggestion, motivation, or expectation of success at arriving at the presently claimed invention.

Finally, Appellant submits that the claimed invention provides unexpected and surprising advantages over the prior teachings in the art. First, the claimed method targets pulmonary T cell

populations in the absence of any substantial effect on peripheral T cells, which is a large advantage over methods which target T cell responses systemically, since peripheral immune responses (i.e., immune responses outside the localized area of delivery, such as in the spleen or lymph nodes) are neither substantially stimulated nor substantially inhibited. Systemically administered antibodies will target all T cells including developing T cells, whereas the aerosolized antibodies of the present invention primarily target T cells at the effector stage, *i.e.* functionally differentiated T cells. The rejection asserts that Lobb et al. meet this claim limitation by teaching that the effect can be achieved without detectable blood levels of antibody (referring to col. 12, last paragraph). However, Lobb et al. merely state at this section of the patent that there were no detectable blood levels of the antibody in the aerosol treated animals. Lobb et al. does not actually demonstrate whether or not the antibody had any effect on any T lymphocytes in the animals. As discussed above, the only teaching of Lobb et al. regarding lymphocytes at all is with respect to Figure 4, where it is shown that anti-VLA4 increases total lymphocytes in the BALF. Even if one assumes, *arguendo*, that aerosolized anti-VLA4 did not substantially affect peripheral T cells, it remains Appellant's position that all evidence in Lobb et al. points to a teaching of an affect on neutrophils and eosinophils, and not lymphocytes, such that there is no teaching or suggestion to arrive at the claimed invention. Moreover, to the extent that the rejection maintains the position that the teachings of Schramm et al. with respect to the systemic administration of antibodies is relevant to the combination of references, it is clear that Schramm et al. do not teach or suggest any advantage of aerosolized antibodies and solely contemplate total systemic depletion of T cells.

Furthermore, in contrast to reports of the administration of other aerosolized antibodies (e.g., anti-IgE administration, described by Fahy et al. (1999, *Am. J. Respir. Crit. Care Med.* **160**:1023-1027)), the present inventors have demonstrated through working examples that the claimed method is highly effective at reducing airway hyperresponsiveness. Finally, evidence has been provided in the present specification that targeting T cells that are present at the allergic site by the localized administration method of the present invention reduces allergic inflammation-associated exacerbation of AHR without affecting the adaptive immune system.

It is noted that Claim 1 is currently restricted to the elected species of αβ TCR, although it is Appellant's position that the non-elected species of γδ TCR, CD3, CD4 and CD8 are also patentable over the cited combination of references, should the rejection be applied to other species, for substantially the same reasons provided herein. With respect to γδ TCR, although Schramm et al. also describe anti-γδ TCR, the teachings of Schramm et al. are thoroughly discussed above, and the consideration of anti-γδ TCR does not render Schramm et al. any more relevant to the combination than when anti-αβ TCR is considered alone, since the deficiencies of Schramm et al., as well as the other references, remain the same. Furthermore, is noted that none of the cited references teach or suggest an antibody that binds to CD3, CD4 or CD8.

However, to be clear, Appellant asserts that the restricted species as set forth by the rejection with respect to αβ TCR, γδ TCR, CD3, CD4 and CD8, do not stand or fall together.

In summary, in view of the discussion above, the combination of references fails to teach or suggest the use of aerosolized antibody that binds to and depletes or inactivates the recited T cells receptors, whereby aerosolized administration of said antibodies reduces airway hyperresponsiveness in a mammal in the absence of substantially stimulating or inhibiting

peripheral T cell responses. Moreover, the combination fails to provide any motivation to make the combination as the rejection has done, or to motivate one to make and use the present invention. Finally, the combination does not provide any expectation of success at making and using the present invention. Therefore, the rejection has not established a *prima facie* case of obviousness in view of the combination of references. In view of the above arguments, Appellant respectfully requests the Board to direct the withdrawal of the rejection of Claims 1, 9-15, 17-18, and 24-35 under 35 U.S.C. §103(a).

**Claim 2**

With respect to Claim 2, Appellant notes that this claim is directed to the elected species of αβTCR, whereas Claim 1 in the group of claims above is directed to all species, including non-elected species that were previously rejoined in the Office Action mailed September 8, 2005, and then subsequently restricted again in the Office Action mailed February 22, 2006. Appellant's arguments against the rejection of Claim 2 under 35 U.S.C. § 103(a) are essentially the same as the arguments presented above in view of Claim 1, although such arguments are in the case of Claim 2 directed exclusively to the elected species. However, in the event that Claim 1 falls as a result of consideration of non-elected species in Claim 1, Appellant expressly submits that Claim 2, as well as dependent Claims 9-15, 17-18, and 24-35, to the extent they depend from Claim 1 with respect to the elected invention of αβTCR as recited in Claim 2, do not stand or fall together with Claim 1.

In view of the above arguments, Appellant respectfully requests the Board to direct the withdrawal of the rejection of Claim 2 under 35 U.S.C. §103(a).

**Claim 16 and Claims 19-23**

In addition to the arguments set forth above for Claims 1, 9-15, 17-18, and 24-35, it is Appellant's further contention that Claims 16 and Claims 19-23 recite particular features of the claimed invention related to advantages of the invention that are not taught or suggested by the combination of references. In particular, Claims 16 and Claims 19-23 recite the use of very low doses of antibody by aerosol administration, which are not taught or suggested by the combination or references, and which it is submitted would be considered to be surprising at the time of the invention. Claim 16 provides the limitation that the antibody is administered at a dose of between about 5 μg antibody and about 10 μg antibody per milliliter of formulation. Claims 19-23 recite doses of less than 40 μg antibody per kg body weight of the mammal (Claim 19), or less than 1 μg per kg body weight of the mammal (Claim 20), or less than 0.5 μg per kg body weight of the mammal (Claim 21), or less than 0.1 μg per kg body weight of the mammal (Claim 22), or less than 20 ng per kg body weight of the mammal (Claim 23).

As taught in the specification, prior to the present invention, it was thought that antibodies delivered by aerosol must be administered in high doses to overcome the effects of expected low potency and to successfully reach the target airways (see page 10, lines 22-26). For example, U.S. Patent 6,165,463 (see Evidence Appendix) indicates that antibodies are considered to be "low potency" drugs, and therefore indicates that fairly high concentrations of antibodies (e.g., in the milligram per milliliter range) should be formulated for aerosol delivery. The publication of Fahy et al. has been discussed above. Indeed, the lowest dose of antibody specifically taught by Lobb et al. (see col. 6, lines 58-62) is 50 μg per kg body weight of the mammal. Lobb et al. also teach that one could provide a dose to "maintain a plasma level of antibody in the range from 1-1000 μg/ml" (col. 6, lines 52-54), but does not state what actual

doses will achieve this range. It is noted that the rejection contends that Lobb et al. specifically teach the dose of Claim 19 (less than 40μg per kg body weight) in col. 6, but such teaching is not found by Appellant. Lobb et al. also teach that the effect of anti-VLA4 (HP1/2) was dose-dependent, and that with intravenous administration, the dose was ineffective below 0.2 mg/kg (col. 12, lines 25-28). Given the teachings in the art at the time of the invention, one would therefore assume that an even higher dose would be needed if the antibody was delivered by aerosol. Delivery of aerosolized antibody in Lobb et al. was provided at 8mg per sheep. Even assuming a 100 kg sheep, this would still be 80 μg per kg body weight. With regard to Schramm et al., this reference does not teach aerosol administration of antibody. With regard to Wigzell et al. and Krause et al., neither of these references demonstrates the delivery of any antibody by any route of administration and provides no specific direction regarding doses for *aerosol* administration. Given the teachings in the art at the time of the invention, such as Fahy et al., it is submitted that one of skill in the art would not expect efficacy in delivering an antibody at the low doses claimed in Claims 16 and 19-23.

In contrast, the method of the present invention is effective at extremely *low* doses of antibody. Indeed, the method of the present invention achieves efficacy with antibody doses that are believed to be about *1000-fold* or more lower than systemic doses of antibody required to achieve the same effect. Doses of antibody as low as 5 μg per ml, delivered by nebulizer to mice in a plexiglass chamber, which would actually deliver much smaller doses to the airway of each mouse, were effective at reducing airway hyperresponsiveness.

The rejection reasons that with respect to the particular recited dosages of formulation or dosage per weight, a "routineer" would initially test a wide variety of different dosages in order

to determine the smallest effective dosage. However, as discussed above, at the time of the invention, it was not generally thought that aerosol delivery of antibodies was efficient or could be achieved at very low doses.

In view of the above arguments, Appellant respectfully requests the Board to direct the withdrawal of the rejection of Claims 16 and 19-23 under 35 U.S.C. §103(a).

**Claim 36**

In addition to the arguments set forth above for Claims 1, 9-15, 17-18, and 24-35, it is Appellant's further contention that the cited combination of combination of references fails to teach or suggest the use of an aerosolized antibody having one of the particularly recited receptor specificities to reduce airway hyperresponsiveness, wherein the binding of the antibody to the receptor causes the depletion or inactivation of the T cell and *wherein any stimulation or inhibition of peripheral T cell responses in the mammal after the aerosolized antibody administration is less than about 10% of stimulation or inhibition of the peripheral T cell responses that would be detected if the antibody formulation was administered systemically*, as claimed in Claim 36. The claimed method targets pulmonary T cell populations in the absence of any substantial effect on peripheral T cells, which is a large advantage over methods that target T cell responses systemically, since peripheral immune responses (i.e., immune responses outside the localized area of delivery, such as in the spleen or lymph nodes) are neither substantially stimulated nor substantially inhibited. Systemically administered antibodies will target all T cells including developing T cells, whereas the aerosolized antibodies of the present invention primarily target T cells at the effector stage, *i.e.* functionally differentiated T cells. The specification demonstrates that aerosolized administration of the recited antibody reduces

airway hyperresponsiveness in a mammal within the claim limitations of Claim 36 (*e.g.,* see Example 5, where any stimulation or inhibition of peripheral T cell responses in the mammal after the aerosolized antibody administration is less than about 10% of stimulation or inhibition of the peripheral T cell responses that would be detected if the antibody formulation was administered systemically).

Appellant refers to the arguments set forth in detail with respect to 1, 9-15, 17-18, and 24-35, and further submit that none of the cited references, alone or in combination, teach or suggest the claimed limitation that any stimulation or inhibition of peripheral T cell responses in the mammal after the aerosolized antibody administration is less than about 10% of stimulation or inhibition of the peripheral T cell responses that would be detected if the antibody formulation was administered systemically. The rejection reasons that Lobb et al. teach that "the effect seen can be achieved without detectable blood levels of antibody...wherein the aerosol administered antibody would therefore not substantially effect peripheral immune T cell responses", referring to col. 12, last paragraph).

However, it is Appellant's position that Lobb et al. merely state in their patent that there were no detectable blood levels of the antibody (*i.e.,* referenced as "the drug") in the aerosol treated animals. Lobb et al. does not actually demonstrate whether or not the antibody had any effect on any T lymphocytes or any other cells in the periphery of the animals, and specifically, Lobb et al. does not teach that stimulation or inhibition of peripheral T cell responses in the mammal after the aerosolized antibody administration is less than about 10% of stimulation or inhibition of the peripheral T cell responses that would be detected if the antibody formulation was administered systemically. Lobb et al. does not perform an experiment to evaluate T cells,

other than to determine that lymphocyte numbers increase in BALF after anti-VLA4 treatment, and has very little disclosure related to T cells at all, and so one can not conclude that Lobb et al. teach the subject matter of Claim 36. Similarly, no such information or evidence is provided in the teachings of Wigzell et al. or Krause et al., and Schramm et al. solely discloses systemic depletion of T cells. Accordingly, it is submitted that the combination of references fails to teach the limitation disclosed in Claim 36, and furthermore, fails to provide any motivation to modify any of the teachings to arrive at the claimed invention.

In view of the above arguments, Appellant respectfully requests the Board to direct the withdrawal of the rejection of Claim 36 under 35 U.S.C. §103(a).

## VIII. CLAIMS APPENDIX

The text of the claims involved in this appeal:

1. A method to reduce airway hyperresponsiveness in a mammal that has, or is at risk of developing, airway hyperresponsiveness, comprising administering to the lungs of said mammal an aerosolized antibody formulation comprising antibodies that selectively bind to a receptor on a T cell selected from the group consisting of: a T cell antigen receptor (TCR) selected from the group consisting of an αβ TCR and a γδ TCR, CD3, CD4 and CD8, wherein the binding of the antibodies to the receptor causes the depletion or inactivation of the T cell, wherein administration of the antibody formulation reduces airway hyperresponsiveness in said mammal; and

wherein the administration of the aerosolized antibody formulation affects pulmonary T cell responses in the mammal, while peripheral T cell responses in the mammal are neither substantially stimulated nor substantially inhibited.

2. The method of Claim 1, wherein said receptor on a T cell is an αβ T cell antigen receptor (TCR).

9. The method of Claim 1, wherein said antibody is a humanized monoclonal antibody.

10. The method of Claim 1, wherein said antibody does not stimulate T cell activation.

11. The method of Claim 1, wherein said antibody is a monovalent antibody.

12. The method of Claim 1, wherein said antibody is a neutralizing antibody.

13. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 500 μg antibody per milliliter of formulation.

14. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 100 μg antibody per milliliter of formulation.

15. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 50 μg antibody per milliliter of formulation.

16. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of between about 5 μg antibody and about 10 μg antibody per milliliter of formulation.

17. The method of Claim 1, wherein said aerosolized antibody formulation comprises less than 35% by weight of said antibody.

18. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 400 μg x kilogram$^{-1}$ body weight of said mammal.

19. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 40 μg x kilogram$^{-1}$ body weight of said mammal.

20. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 1 μg x kilogram$^{-1}$ body weight of said mammal.

21. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 0.5 μg x kilogram$^{-1}$ body weight of said mammal.

22. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 0.1 μg x kilogram$^{-1}$ body weight of said mammal.

23. The method of Claim 1, wherein said aerosolized antibody formulation is administered at a dose of less than about 20 ng x kilogram$^{-1}$ body weight of said mammal.

24. The method of Claim 1, wherein said aerosolized antibody formulation comprises a pharmaceutically acceptable carrier.

25. The method of Claim 24, wherein said pharmaceutically acceptable carrier is selected from the group consisting of: a dry, dispersible powder; small capsules; liposomes; and a nebulized spray.

26. The method of Claim 1, wherein said aerosolized antibody formulation is

administered to said mammal in conjunction with another agent that supports the treatment of AHR selected from the group consisting of: corticosteroids, (oral, inhaled and injected), â-agonists (long or short acting), leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, phosphodiesterase inhibitors, sodium cromoglycate, nedocrimal, and theophylline.

27. The method of Claim 1, wherein said mammal has been sensitized to an allergen and has been exposed to, or is at risk of being exposed to, an amount of said allergen that is sufficient to induce airway hyperresponsiveness (AHR) in said mammal in the absence of said aerosolized antibody formulation.

28. The method of Claim 1, wherein said aerosolized antibody formulation is administered within a time period of between 48 hours or less prior to exposure to an AHR provoking stimulus that is sufficient to induce AHR, and within 48 hours or less after the detection of the first symptoms of AHR.

29. The method of Claim 1, wherein said aerosolized antibody formulation is administered upon the detection of the first symptoms of acute onset AHR.

30. The method of Claim 1, wherein said aerosolized antibody formulation is administered within 1 hour after the detection of the first symptoms of acute onset AHR.

31. The method of Claim 1, wherein said aerosolized antibody formulation is administered within 12 hours or less prior to exposure to a AHR provoking stimulus that is sufficient to induce acute onset AHR.

32. The method of Claim 1, wherein said aerosolized antibody formulation is administered within 2 hours or less prior to exposure to a AHR provoking stimulus that is sufficient to induce acute onset AHR.

34. The method of Claim 1, wherein administration of said aerosolized antibody formulation reduces the airway hyperresponsiveness of said mammal such that the $FEV_1$ value of said mammal is improved by at least about 5%.

35. The method of Claim 1, wherein said mammal is a human.

36. A method to reduce airway hyperresponsiveness in a mammal that has, or is at risk of developing, airway hyperresponsiveness, comprising administering to the lungs of said mammal an aerosolized antibody formulation comprising antibodies that selectively bind to a receptor on a T cell selected from the group consisting of: a T cell antigen receptor (TCR) selected from the group consisting of an αβ TCR and a γδ TCR, CD3, CD4 and CD8, wherein the binding of the antibodies to the receptor causes the depletion or inactivation of the T cell, wherein administration of the antibody formulation reduces airway hyperresponsiveness in said mammal; and

wherein any stimulation or inhibition of peripheral T cell responses in the mammal after the aerosolized antibody administration is less than about 10% of stimulation or inhibition of the peripheral T cell responses that would be detected if the antibody formulation was administered systemically.

## IX. EVIDENCE APPENDIX

A. Fahy et al., 1999, *Am. J. Respir. Crit. Care Med.* **160**:1023-1027 (Submitted in PTO-1449 filed October 4, 2001, and considered by the Examiner on July 17, 2003; cited as evidence by Applicants in Amendment and Response filed May 13, 2003)

B. U.S. Patent No. 6,165,463 (Submitted in PTO-1449 filed October 4, 2001, and considered by the Examiner on July 17, 2003; cited as evidence by Applicants in Amendment and Response filed October 14, 2003).

C. U.S. Patent No. 6,171,799 (Submitted in PTO-1449 filed October 4, 2001, and considered by the Examiner on July 17, 2003; discussed by Applicants in the Specification at page 3).

## X. RELATED PROCEEDINGS APPENDIX

None.

## XI. SIGNATURE OF APPELLANT'S REPRESENTATIVE

Correspondence related to this Appeal Brief should be directed to the undersigned, who may also be contacted at (303) 863-9700.

Respectfully submitted,

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